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REFLECTION PAPER ON THE USE OF PHARMACOGENETICS IN THE PHARMACOKINETIC EVALUATION OF MEDICINAL PRODUCTS

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Reflection Paper on the use of Pharmacogenetics in the Pharmacokinetic Evaluation of Medicinal Products

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1. INTRODUCTION

In recent years a rapid development in our understanding of the genetics behind the interindividual differences in drug action has occurred. This encompasses the area of pharmacogenetics (PG) where the interindividual variability in genes related to drug transporters, drug metabolising enzymes and drug targets is studied in relation to efficacy of drug treatment and adverse drug reactions. A good deal of this variability results from genetic polymorphism, i.e. the occurrence in the same population of multiple allelic states. With respect to pharmacokinetic (PK) aspects, the highest penetrance of genetic polymorphism is registered at the level of drug metabolism where about 40 % of phase I metabolism of clinically used drugs is affected by polymorphic enzymes. The most important polymorphic cytochrome P450 enzymes are CYP2D6, CYP2C19, and CYP2C9. Regarding phase II enzymes, the genetic variability of UDP-glucuronosyltransferases, N-acetyltransferase-2 and some methyltransferases plays a role in the interindividual variability in PK. The additional contribution of polymorphism in drug transporters has recently been recognised.

This reflection paper intends to target the place of PG in the clinical pharmacokinetic evaluation of medicinal products and should be read in connection with the following guidelines:

1) Pharmacokinetic studies in man (Notice to applicants, Vol 3C, C3a, 1987)
2) Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population (EMEA/CHMP/EWP/147013/2004)
3) The investigation of drug interactions (CPMP/EWP/560/95)
4) Note for guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98)
5) Position paper on terminology in Pharmacogenetics (EMEA/CPMP/3070/01)
6) Reflection paper on pharmacogenomic samples and data handling (EMEA/CHMP/201914)
7) A guideline on summary of product characteristics (EMEA/CHMP/64302/2005)

2. SCOPE

The following issues are discussed in the document:

1) In which situations should the effect of PG on PK of new or existing medicinal products be studied
2) At what stage in the clinical development program should PG/PK studies be performed
3) Study design and methodology
4) Evaluation of the clinical consequences of genetic differences in drug substance exposure
5) Special considerations related to drug-drug interactions and impaired or immature organ functions
6) Treatment recommendations based on genetically determined differences in exposure

The broader issue of pharmacogenomics (PGx), i.e. the variability in the entire genome relevant to drug response, will not be considered in this reflection paper.

3. IN WHICH SITUATIONS SHOULD THE EFFECT OF PG ON PK BE STUDIED

PG studies are required for PK evaluation of a new chemical entity if polymorphically expressed proteins are known to be involved in important pathways of metabolism or transport of this compound or pharmacologically active or toxic metabolites, and therefore significantly affecting the local and systemic exposure to these substances.
Furthermore, PG studies involving the identification of novel polymorphic loci are encouraged to be carried out if the compound exhibits important interindividual PK variability, without evident known genetic explanations, likely to affect clinical efficacy and/or safety. Technology has advanced to the point that analysis of genetic factors affecting safety and efficacy of medicines is now fast and reliable. If the genetic locus responsible for PK variability influencing clinical or safety aspects is not evident, it is therefore advisable to carry out genetic analysis of loci likely to be responsible for this variation. In all cases where unexplained PK variation has been identified, samples for pharmacogenetic purpose in further clinical trials, should be collected for future analyses. . This would allow a critical evaluation of the clinical and, if population PK is used, PK consequences of this polymorphism.

For authorized medicinal products, PG/PK studies may still be valuable when new populations, such as children, or higher doses are investigated. Also, PG should be considered when investigating and evaluating the effect of extrinsic and intrinsic factors on the PK of a drug.

Studies of PG differences in the activity and expression of transport proteins involved in drug distribution (efflux or influx) to target organs such as the central nervous system, possibly explaining adverse events or lack of therapeutic effect, is encouraged if there are indications of clinically important differences in these respects and a biologically relevant polymorphism is studied using cohorts large enough to provide power to make appropriate conclusions.

4. AT WHAT STAGE IN THE CLINICAL DEVELOPMENT PROGRAM SHOULD PG/PK STUDIES BE PERFORMED

In general, the importance of PG for the PK of a drug substance may be indicated by *in vitro* data where the proteins involved in human drug metabolism and transport or in the formation, metabolism and transport of pharmacologically active metabolites have been identified. Preclinical animal studies should be interpreted with great caution, as there are usually marked species differences in drug metabolism and transport. If human *in vitro* data suggest major involvement of a protein known to be subject to genetic polymorphism, inclusion of genotyping directed to the candidate gene in early phase I studies is warranted. When the involvement of the polymorphic gene has been verified, *in vivo* studies of the effects of specific polymorphisms on the PK of each of the pharmacologically active compounds likely to contribute to clinical efficacy and/or safety should be considered.

PG/PK studies related to unexplainable PK observations, such as marked interindividual variability or inexplicable outliers, or after observation of clinical efficacy or safety problems suspected to be due to pharmacokinetic variability (see section above), should be performed as early as possible in the drug development program.

When the genotype is predicted or known to markedly affect the PK of pharmacologically active compounds contributing to in vivo efficacy and/or safety, genotyping is encouraged in as many of the phase I, II and III clinical studies as possible to increase the amount of data supporting the recommendations for use in the genetic subpopulation(s). Dose-response studies or other clinical studies

covering the exposure of active substances obtained could be used to support safety and efficacy in a specific genetic subpopulation.

In general, PG should be an integrated part of the clinical study program. Sufficient knowledge should be collected in the phase III studies to satisfactorily clarify the efficacy and safety consequences of the PG-dependent PK differences.

5. STUDY DESIGN AND METHODOLOGY

Conventional PK analysis and population PK analysis
The investigation of the effect of PG on the PK of a drug substance may be performed using a population PK approach in genotyped subjects and patients, or in a conventional PK study. In both cases the study should include a satisfactory number of patients of each genotype in order to obtain valid correlation data. Power calculations should preferentially be done before the initiation of the study. If a genotype is rare, phase I studies with selected inclusion of subjects of this genotype could be useful if feasible. Investigations should focus on mutations/ alterations in genes causing anticipated functional effects on gene expression or function of the gene products, thus resulting in marked alterations in phenotype. Mimicking the absence of a functional protein by an interaction study with a specific inhibitor shown to give full in vivo inhibition of the protein is an alternative but less demonstrative approach.

Genotyping methods and choice of alleles
The genotyping methods should first be validated and then maintained under continuous quality control including the use of standards for the studied polymorphisms as well as blanks for detecting contamination. The analysis should include methods that can identify major genetic variation such as copy number polymorphisms.

6. EVALUATION OF THE CLINICAL CONSEQUENCES OF GENETIC DIFFERENCES IN DRUG SUBSTANCE EXPOSURE

The presentation of the PG/PK results should include a clear description of the alleles studied from biological and genetic perspectives, and a presentation of the pharmacokinetic or clinical parameters studied using appropriate statistics. The clinical consequences of any observed difference in drug exposure in a subpopulation should be based on several factors, such as:

1) the magnitude of the difference in exposure
2) the relationship between drug exposure and clinical effects/adverse effects
3) the severity of the possible adverse events and clinical consequences of loss of efficacy.

The assessment could be based on clinical dose-ranging studies, on pharmacokinetic/pharmacodynamic studies, and on clinical data obtained in the genetic subpopulation and the study population as a whole.
Absence of data on clinical consequences in genetic subpopulations observed or estimated to have a marked exposure difference should be justified and adequately reflected in the SPC.

7. SPECIAL CONSIDERATIONS RELATED TO DRUG-DRUG INTERACTIONS AND IMPAIRED OR IMMATURE ORGAN FUNCTIONS

Drug interactions
Genotyping of the population included in an interaction study is recommended when PG is expected to affect the PK of any of the active substances. Depending on the question investigated, directed inclusion or exclusion of specific genotypes may be useful.

If well known major elimination pathways are absent in a subpopulation, the consequences of inhibition of parallel pathways should be considered.. If the safety consequences of the interaction give an unacceptable risk-benefit for the subpopulation or if sufficient safety data is lacking at such exposures, an interaction study in the subpopulation may be needed for satisfactory treatment recommendations to be possible.

The effect of active substances, which are enzyme or protein inducers, may also be different if the contribution of an enzyme is markedly reduced or absent in a subpopulation. In this case, the net result will depend on the degree of induction -if any- of the parallel pathway. This should be considered especially when a dose recommendation for a certain drug-combination is studied and evaluated.

An increased plasma concentration in genetic subpopulations may lead to more pronounced effects of the investigated drug on other drugs. This should be considered and if necessary were reflected in the recommendations for use of the drug.

Impaired or immature organ function
The consequences of impaired organ function may be different in genetically different subpopulations. This applies mainly if the main elimination pathway in the genetic subpopulation is markedly affected by impaired organ function. This should be discussed by the applicant as well as the need for this to be reflected in the SPC.

The enzymes and transport proteins involved in the PK of a drug substance may be quantitatively and qualitatively different in paediatric patients than in adults as a consequence of developmental gene expression. The most marked differences are expected in newborn infants, infants and toddlers
In addition the effect of polymorphisms may be different in adult than in children.

8. TREATMENT RECOMMENDATIONS BASED ON GENETICALLY DETERMINED DIFFERENCES IN EXPOSURE

Dose recommendations
If there is a need for a dose adjustment, there are several routes that can be applied:

I) Dose titration regardless of genotype
Differences in exposure in genetic subpopulations may be managed by dose-titration in all patients based on safety and/or efficacy markers, or on Therapeutic Drug Monitoring (TDM). If this approach is chosen, the applicant should show that the titration schedule is suitable for the specific subpopulation(s) known to have genetically caused variation in PK as well as for the general patient population.

II) Dosing based on genotype or phenotype
If dose titration is not desirable or feasible and if the safety or efficacy consequences of the exposure difference in the subpopulation are considered a major concern, the phenotype, e.g. based on genotyping, should be carefully ascertained before initiation of therapy.

III) Optional gene based dosing
If variability in drug action is undesirable, e.g. with respect to adverse events affecting quality of life, phenotype based dosing is highly recommended. In such cases the option of improving the benefit/risk via pheno- or genotyping prior to exposure should also be mentioned in the SPC.

Other labelling consequences
In case a suitable dose may not be recommended based on available data, or if other recommendations are more appropriate, this should be reflected in the SPC, e.g. as warnings, contra-indications, etc.

Well-documented functional polymorphism, which has not been studied because of its rare appearance, should be reflected in the treatment recommendations (SPC) if they are likely to influence drug exposure to a clinically relevant extent.

Information about the PK in different genetic subpopulations and, if available and relevant, differences in adverse event profile should be included in the SPC.